

# EXHIBIT 5

## TECHNICAL FEATURE

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FIGURE 1 (LEFT) Typical gowning protocol in a Class 10 cleanroom. FIGURE 2 (RIGHT) Typical gowning protocol in a hospital operating room. Exposed skin is obvious and can be contrasted to semiconductor gowning shown in Figure 1.

# Using Cleanroom Technology Improving Operating Room Contamination Control

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Annually, the CDC reports nearly 99,000 deaths per year resulting from health-care associated infections (HAIs). According to the U.S. Department of Health and Human Services (HHS), it is estimated that of the more than 290,000 incidences of surgical site infection (SSI) annually, more than 13,000 people die each year due to infections acquired during surgical procedures.<sup>1</sup>

In addition to quality of care implications, according to the HHS *Action Plan to Prevent Healthcare Associated Infections*,<sup>1</sup> the added health-care costs of treating SSIs are no longer reimbursed for Medicare patients, placing the financial burden on hospitals. On average, the cost to hospitals per SSI is \$25,546.<sup>1</sup> In aggregate, this amounts to \$7.4 billion in additional health-care costs every year.<sup>1</sup>

It has been estimated that airborne transmission accounts for 10% to 20% of HAIs,<sup>2</sup> although more recent studies have concluded that the role of airborne transmission may be underestimated due to the difficulty of culturing many airborne organisms and the complexities of assessing the role such pathogens play in the contamination of environmental surfaces and subsequent contact transmission.<sup>3</sup> Landmark studies performed

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by Lidwell and his colleagues<sup>4,5</sup> along with many other studies<sup>6,7</sup> have indicated a strong connection between contamination in the air during surgeries and SSI rates. Clinical trials carried out in Britain, Europe, and the United States have confirmed that between 80% and 90% of bacterial contaminants found in the wound after surgery come from colony forming units (cfu) present in the air of the operating theatre.<sup>8</sup> With respect to bacteria transmitted to the surgical site through the air, squames (or skin scales) are the primary source of transmission.<sup>9</sup> Approximately  $1.15 \times 10^6$  to  $0.9 \times 10^8$  squames are generated in a typical two- to four-hour surgical procedure.<sup>6</sup>

Viral and fungal contamination also can be present in these skin scales.

An interesting parallel can be drawn between the control of these airborne contaminants in operating rooms (ORs) and semiconductor manufacturing cleanroom environments. In each case, the design principle of using unidirectional, controlled (often referred to as laminar) airflow to contain and remove airborne particles, particularly in the area targeted as the sterile field, is generally accepted as the most effective method of preventing airborne contaminants from landing in that sterile field. However, cleanroom technology has proven effective in virtually eliminating human particle contamination, vastly improving product yields in the semiconductor manufacturing industry.<sup>10</sup>

This article identifies the differences in air delivery between semi-conductor manufacturing cleanroom and operating room designs, and discusses how employing the single-large diffuser (SLD) configuration used in semi-conductor manufacturing cleanrooms can significantly reduce the incidence of airborne contaminants reaching the patient in an operating room (OR).

There are three basic design concepts evaluated for ceiling-mounted air delivery in a surgical suite: air curtain (AC), multi-diffuser array (MDA) and single-large diffuser (SLD).

The AC design uses a laminar flow diffuser array over the surgical table with a high velocity slot diffuser at the perimeter of the sterile field. The concept is to create a barrier of air from the slot diffusers, protecting the sterile field from contaminants outside of that space. The MDA uses multiple laminar diffuser panels that are set into an array in the ceiling. According to ASHRAE Standard 170-2013, *Ventilation of Health Care Facilities*, minimum guidelines, the supply air array must extend a minimum of 12 in. (305 mm) beyond the footprint of the

operating table, but up to 30% of the area encompassed can be used for non-air delivery devices (booms, light troffers, etc.). Light booms in the air field create blockages in the air, with turbulent zones beneath the lights.<sup>11</sup> Similarly, gaps between diffusers allowed by Standard 170-2013 create turbulent zones beneath the areas where airflow is not being delivered. The SLD design supplies air from a single, large diffuser that concentrates the air delivery in a controlled air field over the surgical table and reduces these turbulent zones.

### Semiconductor Manufacturing Cleanroom Design

Cleanroom and process equipment design has ultimately minimized the human impact through gowning, careful control of filtered airflow directed to protect the product from the human, and product isolation during manufacturing. The trend from 1985 to 2000 shows that the cleanroom and cleanroom workers have been virtually eliminated as sources of contamination, declining from 50% to < 5% of the wafer level contamination. These results in product improvement are despite the decreased circuit line widths by a factor of 85 and the accompanying 17 fold allowable defect density reduction over the same 25-year period (from mid-1970s to ~ 2000.)<sup>10</sup>

One of the first large “state of the art” semiconductor manufacturing cleanrooms was built in the late 1980s in Santa Clara, Calif. It was a radical departure from any cleanroom built previously in the United States. It was an experiment – building a developmental fab incorporating all best known practices in order to evaluate their impact on yield. The project philosophy could be summarized as: “Hey, let’s do this right from the bottom up.”<sup>12</sup> Ultimately, it met yield expectation, achieving better than Class 1 (ISO M1.5) cleanliness by incorporating more efficient HEPA filters (99.9995% efficient), filtering outside air brought into the cleanroom with HEPA and activated carbon filters, and using polytetrafluoroethylene cloth gowns that fully encapsulated the workers. The gowns included helmets with battery-powered fans to draw air in through the helmet face and discharge it below the work surface after passing it through a small HEPA filter. Other features were incorporated to reduce particulate concentration including static dissipative surfaces, perforated work surfaces, mouth rinsing, and pre-gowning protocols to prevent gown and gowning room contamination. There were many additional air delivery process improvements as well that are now

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incorporated into a typical “state-of-the-art” semiconductor manufacturing cleanroom.

To understand how we can use cleanroom technology to improve contamination control in a surgical suite it is important to understand the differences between their respective design elements. The following attributes represent a typical Class 10 (ISO M2.5) Cleanroom:

- Ceiling height (raised floor to filter ceiling) 12 ft (3.7 m);
- 25% minimum/100% maximum HEPA filter coverage (% of ceiling area);
- 99.9995% HEPA filters, ceiling mounted;
- Air recirculation change rate of ~ 90 per hour – 360 per hour;
- Perforated raised floor for optimal vertical laminar flow;
- Filter face velocity of 72 fpm (0.37 m/s);
- Room pressurized to 0.07 in. w.c. (17.4 Pa) above dirty adjacent space;
- Full coverage gowns (*Figure 1*, eyes exposed but with safety glasses, Page 18); helmets with battery-powered fan keeping helmet “negative” used where wafers are exposed to factory environment;
- Further product isolation within mini-environments ~ Class 1 (ISO M1.5) or better;
- Current product line width 0.022 micron (millionth meter); damage can be caused by a particle size ~ 0.002 – 0.004 micron diameter; and
- Control over all aspects of contamination in environment and materials used in manufacturing.

### Operating Room Design

The following attributes are based primarily on Standard 170-2013<sup>13</sup>

minimum guidelines for a modern OR sized 20 ft × 20 ft (6.1 m × 6.1 m):

- Ceiling height between 9 ft and 12 ft (2.7 m and 3.7 m);
- Laminar flow diffuser ceiling air supply grid;
- 99.97% efficient HEPA filters either upstream of the ceiling grid or part of the ceiling grid;
- Ceiling grid size between 6 ft × 8 ft (1.8 m × 2.4 m) and 8 ft × 8 ft (2.4 m × 2.4 m) (12% to 16% ceiling coverage);
- Up to 30% of the ceiling grid area can be devoted to non-airflow delivery (i.e., boom mounts, lights);
- Low wall-mounted return grilles; at least two, 8 in. (203 mm) above the floor in opposite corners; two additional diffusers may be installed near the ceiling in the walls;
- Air change rate of 20 to 25 per hour of which 3 to 4 ach are from outdoor air;
- Laminar diffuser array face velocity of 25 to 35 fpm (0.12 to 0.18 m/s);
- Room pressurized to 0.01 in. w.c. (2.5 Pa) positive to the adjacent space;
- Smocks/scrubs with caps and double gloves – some exposed skin allowed, *Figure 2*, Page 18.
- Typical particle size carrying bacteria ~ 10 micron diameter; and
- No known method to fully control infection from bacteria in OR.

Summarizing the previous hospital OR design and where it differs from semiconductor manufacturing cleanrooms.

- Hospital ORs are not particle- and bacteria-free even when using the prescribed methods of air handling;
- The particles that carry bacteria emanate either from personnel in the room or from the patient or products introduced into the OR;

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- In most cases, OR personnel are not wearing full coverage gowns and hoods when in close proximity with the surgical site as they would be in semiconductor manufacturing cleanrooms when working with exposed wafers;

- Airflow directed at the partially gowned OR personnel can sweep particles toward the surgical site rather than away from it;

- The current air system design does not fully isolate and protect the surgical site from contaminants that may be generated in the rest of the OR during surgery. Major strides in yield improvements occurred in semiconductor manufacturing when the wafer was isolated from the rest of the cleanroom.

- Ceiling filter or laminar diffuser coverage is not 100% resulting in turbulence between the edge of the sterile field and the perimeter walls. Turbulent areas typically have vertical air currents that circulate particulate.

- Air leaves the space through only a limited number of outlets—two to four outlets in only two walls are prescribed—rather than through a perforated floor leading to airflow turbulence in parts of the room and unpredictable particle movement.

- Space pressurization is low—only 0.01 in. w.c. (2.5 Pa) to the adjacent space. It has been recognized that when doors are opened, pressurization effectiveness is lost. This is not the case with semi-conductor cleanrooms that operate at higher pressures—up to 0.07 in. w.c. (17.4 Pa) and/or use air locks.

- There are many solid objects in the OR that deflect the laminar air leading to unpredictable, random particle movement. In semiconductor cleanrooms, wherever possible,

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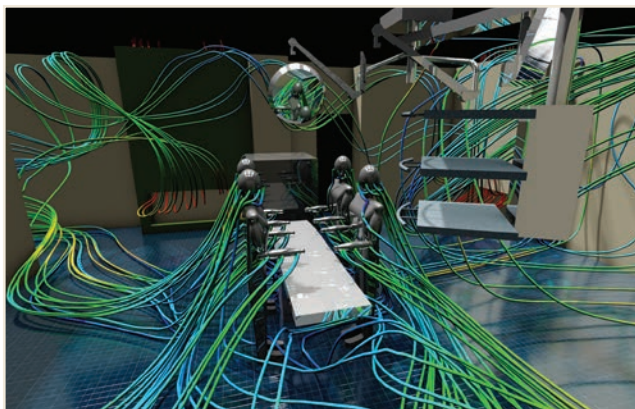
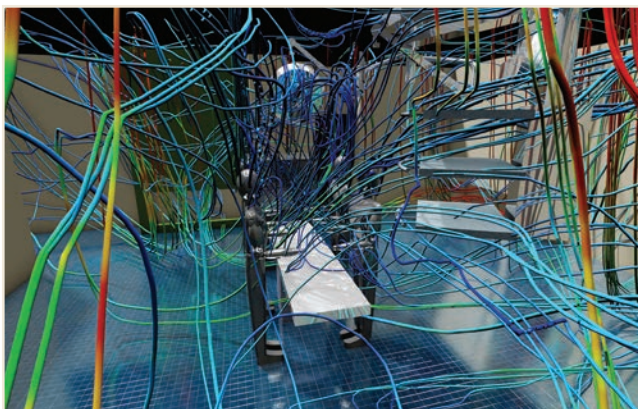


FIGURE 3 CFD particle trace. (Left) Particle trace shows chaotic dispersion of contaminants in an MDA system that meets ASHRAE Standard 170 guidelines. (Right) At the same conditions, particle trace shows efficient and settled movement of contaminants away from the surgical team in a SLD system.



FIGURE 4 Airflow visualization smoke study. (Left) Smoke visualization study shows turbulent, upward moving column of air under diffuser with 2 in. square blanked off area. (Right) Smoke visualization shows controlled, downward movement of air under unobstructed diffuser.

seats, benches, and work surfaces are perforated to aid particulate flow out of the cleanroom.

- Use of makeup by OR personnel is not universally prohibited, but it is not allowed in semiconductor manufacturing cleanrooms because it is a source of contamination.

Another important difference, beyond the scope of this article but worth mention, is the typical construction methods used for hospital ORs and cleanrooms. Whereas a hospital OR is typically built-up on site, semiconductor manufacturing cleanrooms are generally installed taking maximum advantage of factory fabrication in a controlled environment to reduce on-site contamination, construction timelines, labor, and the coordination of trades.

### Comparing OR Design Performance

Referring back to the introduction, three basic design concepts for ceiling-mounted air delivery in a surgical suite have been evaluated: air curtain (AC),

multi-diffuser array (MDA), and single-large diffuser (SLD).

Each of these designs is considered to provide unidirectional, controlled airflow based on the type of diffuser being used. However, the application of these diffusers can vary widely and consequently influence the performance of each of these systems.

The methods used to study and compare the performance of OR designs in terms of particle movement in and around the sterile field included:

- Computational fluid dynamic modeling (CFD);
- Airflow simulation (smoke studies, neutral buoyancy bubbles, etc.); and
- Particle and microbial sampling.

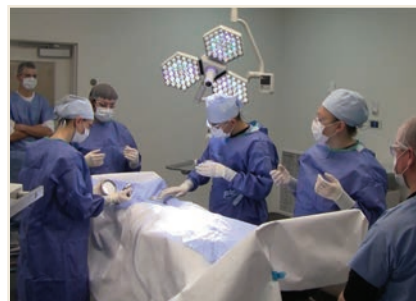
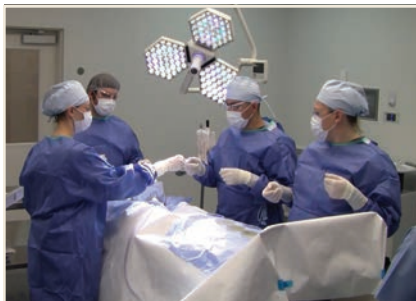
For each method, the systems were compared using the same room conditions (temperature, airflow velocity, airflow changes) and the same room design (returns, equipment placement). Where applicable, OR occupant placement and activity, in addition to the thermal properties of personnel, the patient and equipment also were

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FIGURE 5 Mock operating room and surgery.



kept constant for each method. The only difference in each case was the design of the diffuser system in the area above the operating table.

Using CFD, Figure 3 (Page 22) demonstrates how airflow patterns in the OR can impact particle induction and migration. For example, particle trace analysis of the MDA design as compared to the SLD reveals that the SLD performs much better in terms of pulling contaminants away from the surgical site with all other conditions being equal.

Smoke studies indicate the influence of low pressure zones that are created from blocking the air. As shown in Figure 4 (Page 22), blocking the airflow at the diffuser creates a zone of upward moving, turbulent airflow. The picture on the right shows downward moving controlled airflow where no blockage is present.

Although CFD analysis and smoke studies can give us an important look at airflow, to really understand how each design affects submicron sized contaminants at the surgical site we need to do particle and microbial sampling during surgery. Given the inherent limitations of duplicating every aspect of three individual surgeries to provide a comparison of each design, in addition to patient quality of care concerns, this type of sampling has been done in a simulated OR environment during a mock surgery. In January 2013, the author led a study that evaluated the SLD design against the conventional AC and MDA operating room designs (Figure 5).<sup>14</sup> This testing was conducted in a fully-functional operating room mockup, constructed in compliance with current FGI Guidelines,<sup>15</sup> and ASHRAE Standard 170. The room

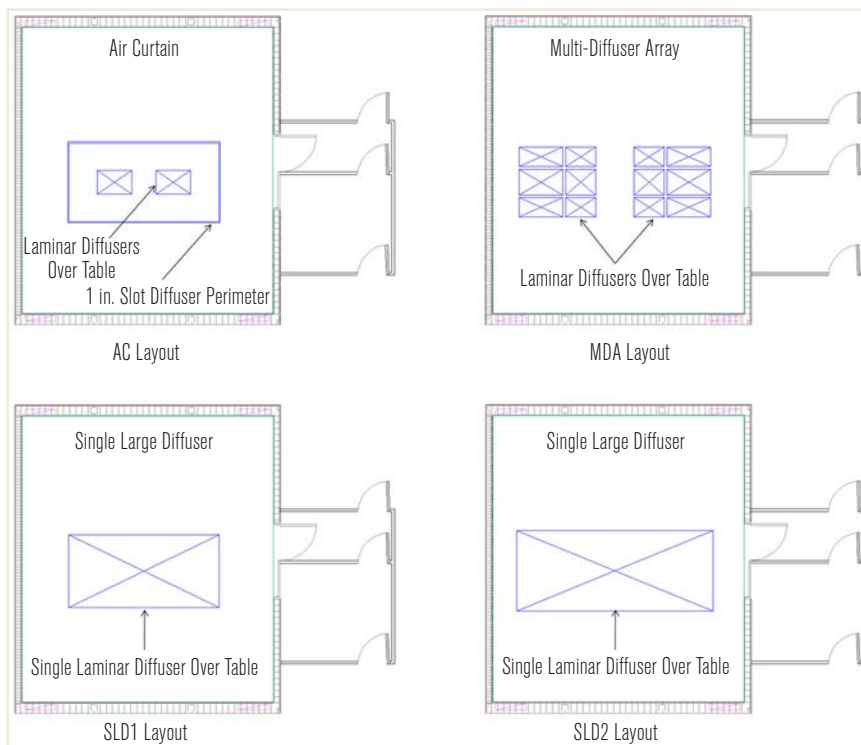


FIGURE 6 Air delivery scenarios.

TABLE 1 Airflow configurations.							
LAYOUT	AREA (SF)	VELOCITY (FPM)	CFM	ACH*	VELOCITY (FPM)	CFM	ACH
AC	11/3	27/93	576	7.2	NA	NA	NA
MDA	57	30	1,700	21.2	50	2,828	35.2
SLD1	57	30	1,700	21.2	50	2,828	35.2
SLD2	86	30	2,580	32.1	50	4,270	53.2

Note: AC layout = 11 ft<sup>2</sup> of laminar diffuser, 3 ft<sup>2</sup> of slot diffuser, 27 fpm from laminar diffuser, 93 fpm from the slot diffusers. The AC layout was tested at only one air volume. \*Air Changes per Hour (ach) based on room volume.

was held at a pressure of 0.01 in. w.c. (2.5 Pa) and a temperature of 62°F (17°C) during the testing. The air delivery system used HEPA filters that were sealed above the OR ceiling and was configured with the ability to have diffusers changed out from within the room without

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contaminating the space. The room dimensions were 20 ft 5 in. W × 20 ft 7 in. L × 10 ft H (6.2 m W × 6.3 m L × 3.0 m H).

Because a standardized testing method for airborne contaminants in an OR does not exist, the experimental design for sample collection, laboratory analysis and data interpretation were derived from the United States Pharmacopial Convention, USP<797> (Revision Bulletin 2008 guidelines for pharmaceutical sterile compounding facilities)<sup>16</sup> with one exception; in this experiment samples were collected during the simulation of an active surgical procedure as opposed to an unoccupied room. The mock OR was precisely measured and marked for repeatable placement of the surgical equipment and team members, a manikin (to simulate the patient on the operating table), and all particle measurement equipment. Surgical procedures were scripted to mimic an actual surgery as well as the process for bringing in new instruments during a surgical operation. Each team member was assigned a predesignated task to complete at a specific time during each test conducted. The manikin was equipped with two mock surgical sites, one at the chest and one at the legs. Passive samples were collected at the chest site and active samples were collected at the leg site. The chest and leg sites were heated to constant temperatures of 98°F and 75°F (36.7°C and 23.9°C), respectively to simulate the warm air plume emitted from a surgical site.

Four different ceiling air delivery scenarios, each meeting ASHRAE Standard 170 guidelines for diffuser coverage over the patient table, were tested (*Figure 6*, Page 24). The air curtain was tested at 27 fpm (0.14 m/s) velocity from the diffuser screens, and the slots were between 85 fpm and 100 fpm (0.43 m/s and 0.51 m/s) (*Table 1*, Page 24). The three remaining scenarios were tested at 30 fpm (0.15 m/s) air velocities, with additional tests performed at 50 fpm (0.25 m/s). The MDA and SLD1 scenarios were equipped with the same diffuser face area (57 ft<sup>2</sup> [5.3 m<sup>2</sup>]) and airflow was delivered at the same volumetric flow rate. The SLD2 diffuser face area was approximately 30 ft<sup>2</sup> (2.8 m<sup>2</sup>) larger than the MDA and SLD 1 scenarios.

Each scenario consisted of three repeatable experiments, exactly 15 minutes in duration, conducted over approximately 70 minutes. A controlled microbial

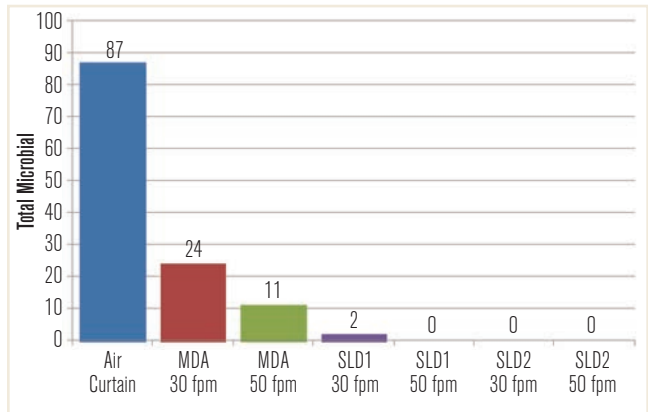


FIGURE 7 Microbial results, reported as colony forming units per cubic meter (cfu/m<sup>3</sup>).

contaminant (yeast) was introduced for each 15-minute experiment (as described in Reference 14) in the exact same quantity with steps taken in between each experiment, including scrubbing, gowning and OR cleaning in accordance with operating room prepara-

tion procedures, to ensure that only that quantity was present in the OR for each experiment.

The microbial data collected during the study is summarized in *Figure 7*.

No microbial contamination was detected with the SLD1-50, SLD2-30 or SLD2-50 configurations which meets the ISO Class 5 pharmaceutical cleanroom standard (*Table 2*).<sup>17</sup> SLD1-30 met ISO Class 7, while all other designs met ISO Class 8, with greater than 10 cfu/m<sup>3</sup>. The data also indicates that at equal size and airflow, a one or two ISO Class improve-

ment was achieved between the MDA and SLD1 scenarios without additional energy consumption.

## Conclusion

Preventing airborne contaminants from settling in the desired sterile field is an important objective for the airflow system in both ORs and semiconductor/pharmaceutical manufacturing facilities. What is missing for ORs is an aerobiological standard conceptually similar to that used in manufacturing cleanrooms. The fact that an operating room presents a much more dynamic environment than a semiconductor manufacturing facility, along with the unlikelihood that doctors, nurses and other OR personnel will be required to wear full coverage clothing to prevent release of squames into the OR,

TABLE 2 Recommended action levels for viable particles in air.

ISO CLASS	ACTIVE AIRBORNE (CFU/M <sup>3</sup> )*
5	>1
7	>10
8	>100

\*For each ISO Class, mitigation that may include investigation of the contaminating source and additional cleaning is required by USP 797 standards when the number of colony forming units per cubic meter detected in the air is greater than the allowable number for that ISO Class.

means that more airborne contaminants are released into an OR during surgery than are released into a working semiconductor manufacturing facility. Therefore, the role of airflow in maintaining a sterile field becomes even more critical for ORs.

What these comparisons and data demonstrate is that concentrating uniform, laminar air delivery over the operating table in an SLD configuration—without the gaps in airflow allowed by ASHRAE Standard 170—can result in predictable airborne particle movement away from the area of the patient in an operating room. The data indicate that airborne contaminants at the surgical site can be considerably reduced, and this reduction can be achieved without increasing energy consumption. The studies have been initiated by the authors with the intent of generating dialog for further investigation to advance the hospital OR environment for the benefit of patients and hospitals.

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Mock OR equipment and services donated by Lighthouse Worldwide Solutions (particle counters), Trumpf Medical (equipment/light/monitor booms), Ergotron (medical carts), Skytron (surgical table), Forbo (OR flooring), NorthWest Engineering (validation service).

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